

# Impact of Pharmacy-led Dyslipidemia Interventions on Medication Safety and Therapeutic Failure in Patients

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## Abstract

**Objectives:** The researchers sought to assess the impact of pharmacologic intervention on previously identified patients with coronary heart disease (CHD), diabetes, or multiple risk factors who experienced therapeutic failure in treating hyperlipidemia. The study also sought to evaluate changes in medication usage patterns, including rates of unsafe combination therapies before versus after the interventions, and reevaluate the analyses of barriers to effective treatment, including safety concerns. **Methods:** An ad hoc report was run on patients with hyperlipidemia from August 2002 through January 2003. Patients were then matched to the 527 patients identified from the previous lipid study as experiencing therapeutic failure. Primary endpoints included comparisons of the most current LDL value to previous LDL values, as well as changes in lipid-lowering therapies, combination regimens, and goal-attainment rates. **Results:** Statistically significant reductions in LDL were noted for patient subgroups in the CHD or CHD-risk-equivalent category, as well as the multiple risk factor category. These reductions amounted to a 33.6 mg/dL (24.4 percent) LDL reduction among CHD or CHD-risk-equivalent patients, and a 41.05 mg/dL (26.1 percent) reduction in LDL among those in the multiple risk factor category. Of the 310 patients with previous treatment failure whose goal attainment was reviewed, LDL values were available for 255 patients. Of these patients, 175 (68.6 percent) were now at LDL goal, compared to none from the previous review. This result was statistically significant ( $P < 0.001$ ). Organized by risk category, LDL goal attainment showed a 53.2 percent increase among the 109 highest risk (CHD or CHD-risk-equivalent) patients and increased 80.1 percent among 146 multiple risk factor patients. Average LDLs were reduced by 38 mg/dL in all patients and by an average of 41 mg/dL among the highest risk category patients. **Conclusion:** Results demonstrated significant improvements in LDL values among patients with previous therapeutic failures after implementation of a variety of pharmacy interventions.

## Introduction

Medication safety is a national imperative that warrants pharmacy leadership on strategies and interventions to prevent errors. Medication safety initiatives published in the literature often describe the impact a program has on reducing errors; however, few studies have quantified error reduction into patient outcomes

Report Documentation Page			Form Approved OMB No. 0704-0188		
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1. REPORT DATE <b>MAY 2005</b>		2. REPORT TYPE <b>N/A</b>		3. DATES COVERED <b>-</b>	
4. TITLE AND SUBTITLE <b>Impact of Pharmacy-Led Dyslipidemia Interventions on Medication Safety and Therapeutic Failure in Patients</b>				5a. CONTRACT NUMBER	
				5b. GRANT NUMBER	
				5c. PROGRAM ELEMENT NUMBER	
6. AUTHOR(S)				5d. PROJECT NUMBER	
				5e. TASK NUMBER	
				5f. WORK UNIT NUMBER	
7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES) <b>Agency for Healthcare Research and Quality Office of Communications and Knowledge Transfer 540 Gaither Road, Suite 2000 Rockville, MD 20850</b>				8. PERFORMING ORGANIZATION REPORT NUMBER	
9. SPONSORING/MONITORING AGENCY NAME(S) AND ADDRESS(ES)				10. SPONSOR/MONITOR'S ACRONYM(S)	
				11. SPONSOR/MONITOR'S REPORT NUMBER(S)	
12. DISTRIBUTION/AVAILABILITY STATEMENT <b>Approved for public release, distribution unlimited</b>					
13. SUPPLEMENTARY NOTES <b>Published in Advances in Patient Safety: From Research to Implementation. Volumes 1-4, AHRQ Publication Nos. 050021 (1-4). February 2005. Agency for Healthcare Research and Quality, Rockville, MD. <a href="http://www.ahrq.gov/qual/advances/">http://www.ahrq.gov/qual/advances/</a>.</b>					
14. ABSTRACT					
15. SUBJECT TERMS					
16. SECURITY CLASSIFICATION OF:			17. LIMITATION OF ABSTRACT <b>UU</b>	18. NUMBER OF PAGES <b>12</b>	19a. NAME OF RESPONSIBLE PERSON
a. REPORT <b>unclassified</b>	b. ABSTRACT <b>unclassified</b>	c. THIS PAGE <b>unclassified</b>			

and pharmacoeconomics in the form of cost-avoidance. Preventing prescribing errors is a challenge for the Department of Defense (DoD) since a large proportion of military retirees obtain prescriptions from providers not on the base. Efforts to improve medication safety require extensive efforts to reach out to prescribers in the community, patients, and other ancillary health care providers servicing DoD patients. In January 2002, medication safety parameters focusing on prescribing errors and subsequent patient outcomes was identified as a top priority for the DoD Department of Pharmacy. To demonstrate pharmacy impact on patient outcomes, efforts were focused on the most costly and prevalent disease state: cardiovascular illness.

The Patrick Air Force Base (FL) Pharmacy Service conducted a baseline lipid review of patients experiencing therapeutic failure in 2002. Such patients were identified by a hyperlipidemia quarterly provider report identifying all individuals with coronary heart disease (CHD) or diabetes, as well as multiple risk factor category patients who were not at targeted low-density-lipoprotein (LDL) goals. Overall, 6,421 patients were identified through the DoD hyperlipidemia provider report as either experiencing a therapeutic failure or not having an LDL measurement performed within the past year. A barrier analysis was then conducted on information from the 527 patients with LDL lab results and medication records available through the Composite Health Care System (CHCS) computer system. Results from this lipid review identified several important barriers to effective treatment, which fell into four categories: (1) More than half (57.3 percent) of patients not at their LDL goal were undertreated or nonadherent to therapy. This included patients previously on cerivastatin who were no longer on therapy. (2) Suboptimal dosing or lack of titration for those on monotherapy was also identified as a potential opportunity to optimize care. The review identified 31.7 percent of patients on therapy at a subtherapeutic dose. (3) Medication safety, defined as unsafe combination regimens that warranted the Food and Drug Administration (FDA) to require changes in the package insert of simvastatin, was found to be a significant problem. In this safety analysis, 14.7 percent of patients on simvastatin were on combination regimens. Of these patients, almost all (96.4 percent) were on doses of simvastatin that exceeded the safety limit of 10 mg/day. This included two patients on the highest doses of simvastatin, 80 mg, who were on combination regimens with either a fibric acid derivative or niacin. (4) A final analysis looked at therapeutic selection, whether treatment incorporated the Pharmacoeconomic Center (PEC) guidelines on therapeutic failure. Such guidelines recommend atorvastatin as an alternative agent in patients who had a bona fide failure on simvastatin. Failures requiring atorvastatin as an alternate agent were defined as (a) patients not at their LDL goal on maximal doses of simvastatin, (b) patients with an LDL greater than 195 mg/dL or requiring a greater than 50 percent LDL reduction, and (c) patients on combination therapy with simvastatin doses that exceed FDA safety recommendations (simvastatin dose more than 10mg/day in combination with fibrates or niacin).

A pharmacoeconomic analysis was also conducted, which revealed approximately \$6 million was spent annually on direct pharmaceutical costs for patients experiencing therapeutic failure for hyperlipidemia. Extrapolations of

medical expenditures for cardiac hospitalization indicated an additional expenditure of \$9.5 million in the next 5 years because of these therapeutic failures. Such economics revealed a high potential for cost avoidance through optimization of care and outcomes.

Subsequent to this review, the Department of Pharmacy implemented numerous interventions to address this population of lipid failure patients. Therefore, the objective of the present study was to measure the impact of 6 months of pharmacy interventions on patient safety and outcomes through analysis of laboratory values and medication usage patterns.

## **Description of interventions**

Interventions implemented by the pharmacy department, with the support of the medical staff and local Pharmacy and Therapeutics (P&T) Committee were multiple. Patients seen by only off-base (community) providers had access only to one HMG-CoA reductase inhibitor (simvastatin), while on-base providers had a means to provide their patients with alternative (nonformulary) agents when indicated. The first step was development of available services for off-base or community providers that would increase both medication access and enhance patient safety. Therefore, a pharmacist-run patient education/polypharmacy clinic was developed. This clinic served as one venue to support medication access issues and address patient nonadherence to medications. Furthermore, close on-base pharmacy-provider interaction led to the initial stages of development of a lipid clinic, including recruitment of a dedicated clinical pharmacist to run the clinic. The lipid clinic would be a service available to both on-base providers as well as community physicians. Until the lipid clinic was implemented, the patient education/polypharmacy clinic served as the primary communication means for external, community providers requesting nonformulary drugs as well as referrals to the clinic. The polypharmacy clinic was stocked with a variety of patient education materials concerning cardiovascular disease and patient compliance, as well as materials on other disease states and medicines.

Internal mechanisms to prevent potentially dangerous drug interactions were also in place. The protocol relied heavily on a pharmacy technician identifying these interactions with the use of the host pharmacy computer system. Since FDA labeling changes for unsafe combination regimens with simvastatin, the DoD's preferred statin, were just released, all pharmacists were educated on how to deal with such interactions when patients were requesting prescription fills at the pharmacy window. Therefore, a more direct patient intervention entailed having pharmacists, in the course of their normal daily dispensing activities, call physicians to intervene on potentially unsafe drug interactions with the combination regimens. All pharmacists were provided with guidelines on recommendations for therapeutic alternatives, including access to nonformulary agents if needed.

The physician and external health care provider awareness campaign began soon thereafter, which entailed a series of three educational programs led by the chief of pharmacy. The programs were presented throughout the community.

They disseminated baseline results and discussed medication access issues, highlighting pharmacy services and interventions (i.e., polypharmacy and lipid clinics), and mechanisms to access such clinics to enable easier provider-pharmacy communication. The clinical pharmacist in charge of the polypharmacy/patient education clinic was also present to discuss referrals and communication systems. Programs reaching out to community providers also included new cardiovascular updates surrounding dyslipidemia by a well-known, community cardiologist. The partnership with community physicians on medication access issues encouraged community physicians to contact the polypharmacy clinic to refer patients back to the base to have a nonformulary medication considered and dispensed if appropriate. The chief of medical services at the facility pledged to assist community providers by providing them the “tools” to provide the care our beneficiaries deserve. Also, pharmaceutical industry representatives used analyses from the data to help promote the clinic’s service to off-base providers. In fact, this partnership with industry was indispensable in marketing the clinic to off-base providers during representatives’ normal detailing visits.

## **Methods**

Six months after beginning the interventions, a report was done on patients with hyperlipidemia. Patients were then matched to the 527 patients at Patrick Air Force Base who had been identified in the baseline lipid analysis as experiencing therapeutic failure. Primary endpoints included comparisons of the most current LDL value to previous LDL values, as well as changes in lipid-lowering therapies, combination regimens, and goal-attainment rates among previous patients experiencing therapeutic failure. Since the original, baseline therapeutic failure report that identified all patients who were not at targeted LDL goals included only CHD/CHD-risk-equivalent and multiple risk factor category patients, goals of less than 100 mg/dL for CHD patients and less than 130 mg/dL for multiple risk factor patients were used. Again, based on data availability from the original therapeutic failure report, patients with one or no factors were not included in the analysis. Data variables consisted of the National Cholesterol Education Program—Adult Treatment Panel III (NCEP—ATPIII) risk category, most recent LDL level, previous LDL level when patients were flagged as having therapeutic failure, last lipid-lowering agent filled, rates of combination therapies, medication doses, percent LDL reduction needed to reach LDL goal, and pharmacotherapy at the time patient was identified as a therapeutic failure. A custom built Microsoft® Access database was used for data analysis. Statistical analysis consisted of paired *t*-tests to compare current and previous LDL values. Chi-square analysis was used to compare goal-attainment rates among CHD and multiple-risk-factor category patients before and after the pharmacy interventions. MiniTabs® software was used for all statistical analyses. A *P*-value of less than 0.05 was considered statistically significant.

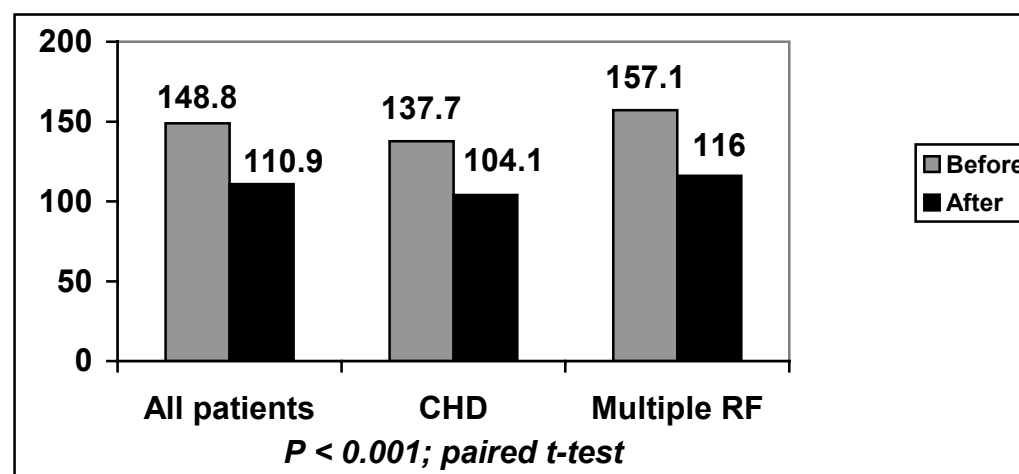
## Results

From the previous DoD hyperlipidemia report that identified patients as either experiencing a therapeutic failure or not having an LDL test performed within the past year, 527 patients had medical records available through the DoD CHCS system and subsequently were included in the original barrier analysis. Of these 527, 6-month follow-up data was available for 310 patients (59 percent), who were therefore included in this follow-up study. Of the 310 patients reevaluated, 143 (46.1 percent) were in the CHD or CHD-risk-equivalent category requiring an LDL goal of less than 100 mg/dL. The multiple risk factor group requiring an LDL goal of 130 mg/dL consisted of 167 (53.9 percent) patients.

Results demonstrated a statistically significant reduction in LDL value for all patients after the interventions ( $P < 0.001$ , paired  $t$ -test). This amounted to a 37.87 mg/dL reduction in LDL, or 25.5 percent reduction. When broken down by risk category, statistically significant reductions in LDL were noted for patient subgroups in the CHD or CHD-risk-equivalent category as well as multiple risk factor category. These reductions amounted to a 33.6 mg/dL (24.4 percent) LDL reduction among CHD or CHD-risk-equivalent patients, and a 41.05 mg/dL (26.1 percent) reduction in LDL among those in the multiple risk factor category (Figure 1).

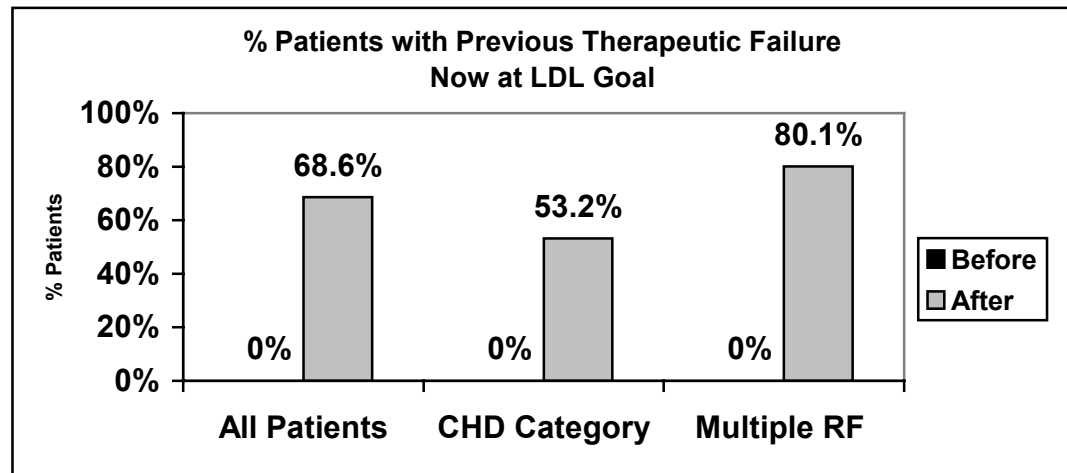
LDL goal attainment was also analyzed. Of the 310 patients reviewed, LDL values were available for 255 patients. Of these patients, 175 (68.6 percent) were now at LDL goal, compared to none from the previous review, which included only patients whose therapies had failed. In breaking down patients into risk categories, LDL goal attainment was increased to 53.2 percent (58 of 109 patients) among the highest risk—CHD or risk-equivalent patients—and 80.1 percent (117 of 146) among multiple-risk-factor category patients (Figure 2).

**Figure 1. Comparison of LDL value before vs. after the interventions**



CHD = coronary heart disease; RF = risk factors

**Figure 2. Percent of patients with previous failure now at LDL goal**



CHD = coronary heart disease; RF = risk factors;  $P < 0.001$ ; chi-square

From the baseline analysis, barriers to effective treatment were broken down into the following four major categories:

1. Undertreatment or patient nonadherence to lipid-lowering therapy;
2. Suboptimal dosing or failure to titrate;
3. Combination regimens and safety; and
4. Therapeutic selection.

A reevaluation was conducted of these previous barriers to goal attainment. The baseline review revealed 302 patients (57.3 percent) nonadherent to therapy or previously on cerivastatin and not on renewed pharmacotherapy (Category 1 patients). The follow-up review included 159 matched patients from the original 302 Category 1 patients. Of these 159 patients who were not on pharmacotherapy or on cervistatin without renewals, 155 (97.5 percent) were now on therapy, and LDL values were available for 118 of these patients. Current average LDL level was statistically significantly lower after the interventions compared to baseline ( $P < 0.001$ ) and represented a 57.24 mg/dL reduction (36.6 percent) in average LDL (156 mg/dL versus 99 mg/dL ( $P < 0.001$ ; paired  $t$ -test).

Patients on monotherapy with suboptimal dosing or lack of dose titration were classified as Category 2 patients. From the baseline barrier analysis, 167 patients or 31.7 percent received subtherapeutic doses. In this follow-up analysis, 151 patients were matched to the 167 previous Category 2 patients for dose titration assessments. Results demonstrated changes in medication or dose titrations in 71 (47 percent) of these 151 patients identified from the previous review as having suboptimal dosing. Table 1 (above) outlines a detailed summary of prior and current therapies for Category 2 patients. LDL values were available for 121 of the 151 patients analyzed as Category 2 patients. Results demonstrated a 24.7

mg/dL reduction (17 percent) in average LDL level among these patients (145 mg/dL versus 120 mg/dL;  $P < 0.05$  paired  $t$ -test).

**Table 1. Previous versus current therapies for patients previously identified as receiving suboptimal monotherapy**

Previous Drug	Dose/Day	Current Therapy	Dose/Day	Intervention	No. of Patients (n=151)
simvastatin	20	No Therapy	0	Discontinuation	4 (3%)
simvastatin	20	Gemfibrozil	600	med changed	2 (1.3%)
simvastatin	10	Gemfibrozil	600	med changed	1 (0.7%)
simvastatin	40	Gemfibrozil	600	med changed	2 (1.3%)
simvastatin	20	atorvastatin	20	med changed	3 (2%)
simvastatin	10	atorvastatin	10	med changed	1 (0.7%)
simvastatin	10	atorvastatin	20	med changed	5 (3.3%)
simvastatin	20	atorvastatin	10	med changed	5 (3.3%)
simvastatin	40	atorvastatin	20	med changed	1 (0.7%)
simvastatin	40	atorvastatin	40	med changed	1 (0.7%)
simvastatin	10	Niaspan	500	med changed	1 (0.7%)
simvastatin	10	Niaspan	1000	med changed	1 (0.7%)
simvastatin	40	Niaspan	500	med changed	2 (1.3%)
simvastatin	20	Niaspan	500	med changed	2 (1.3%)
simvastatin	20	fenofibrate	160	med changed	2 (1.3%)
simvastatin	10	fenofibrate	160	med changed	4 (3%)
simvastatin	40	simvastatin	20	dose decrease	14 (9.3%)
simvastatin	40	simvastatin	80	dose increase	6 (4%)
simvastatin	40	simvastatin	40	no change	18 (11.9%)
simvastatin	10	simvastatin	10	no change	6 (4%)
simvastatin	20	simvastatin	20	no change	33 (21.85%)
simvastatin	10	simvastatin	20	dose increase	4 (3%)
simvastatin	10	simvastatin	40	dose increase	8 (5.3%)
simvastatin	20	simvastatin	80	dose increase	4 (3%)
simvastatin	40	simvastatin	80	dose increase	1 (0.7%)
simvastatin	20	simvastatin	10	dose decrease	5 (3.3%)
simvastatin	20	simvastatin	40	dose increase	14 (9.3%)
simvastatin	10	simvastatin	20	dose increase	1 (0.7%)



Changes to the simvastatin package insert recommend prescribing no greater than 10 mg of simvastatin when used with fibrates or niacin.<sup>1</sup> An assessment of medication safety from this labeling change was evaluated in all patients defined as Category 3. From the previous review, 28 of 191 patients (14.7 percent) on simvastatin were on adjunctive therapy. In the reevaluation, 230 of 310 patients total were on simvastatin. The overall rate of add-on or combination therapy with simvastatin was 10.4 percent (24 of 230 patients), a reduction of 4.3 percent from the previous review. In the previous review, 96.4 percent of all patients (27 of 28) prescribed combination therapy with simvastatin were on doses of simvastatin that exceeded the safety limit of 10 mg/day. For this follow-up analysis, 87.5 percent of such patients (21 of 24) on combinations were on unsafe doses, therefore presenting opportunities for continued interventions to target unsafe combination regimens. An evaluation of matched patient samples identified from the baseline review as being on an unsafe combination regimen was reevaluated for any changes in pharmacotherapy. Of the 27 patients on combination regimens from the previous review, 12 patients were matched in our current analysis. Results showed safety changes occur in 67 percent or 8 of these 12 patients previously on unsafe combination regimens.

Category 4 incorporates treatment selection according to PEC guidelines on therapeutic failures. Such guidelines recommend atorvastatin as an alternative agent in patients who have a bona fide failure on simvastatin. Failures included in this review consist of (a) patients not at LDL goal on maximal doses of simvastatin (80 mg), (b) patients with an LDL level greater than 195 mg/dL or requiring a greater than 50 percent LDL reduction, and (c) patients on combination therapy with simvastatin doses that exceed FDA safety recommendations (simvastatin dose > 10mg/day in combination with fibrates or niacin). From the prior baseline review, 32 percent of patients (72 of 225) on pharmacotherapy qualified for atorvastatin usage. The follow-up review demonstrated only 9 percent (28) of the remaining patients were candidates for atorvastatin after the interventions were implemented.

Overall, utilization increased from less than 1 percent (0.19 percent) to 9 percent based on PEC guidelines for appropriate atorvastatin prescribing (Table 2). For those patients converted to atorvastatin, the average LDL reduction was 44 mg/dL (28 percent) from the previous therapy (157 mg/dL versus 113 mg/dL;  $P < 0.01$  paired  $t$ -test).

Results demonstrated significant improvements in LDL values among patients with previous therapeutic failure after implementation of numerous pharmacy interventions. On average, LDL was reduced by 38 mg/dL in all patients. Among the highest-risk category patients, LDL values were reduced by an average of 41 mg/dL. In contrast to the previous 6-month review where no patients were at LDL goal, substantial improvements occurred, with 68.6 percent of patients now at their LDL goal. Previous barriers toward goal attainment were readdressed, illustrating improvements in all defined areas in the barrier analysis. Almost all evaluated patients who were previously lacking pharmacotherapy were now on therapy. Approximately half the patients who lacked adequate dose titrations

either had their dose subsequently titrated or medication changed. Potential unsafe combination regimens also declined from a 15 percent simvastatin add-on medication rate to 10.4 percent. Opportunities to intervene on unsafe combination regimens still existed though, with approximately 9.1 percent of simvastatin therapy patients on unsafe combination regimens. However, the majority of this 9.1 percent reflected new initiations rather than patients targeted from the prior review. When evaluating patients from the prior review who were on unsafe combinations, 67 percent of patients had their prior therapies changed to a safer alternative. Thus, only three patients remained on an unsafe regimen. The previous analysis identified 32 percent of potential candidates for atorvastatin based on PEC criteria. Since the reevaluation, atorvastatin utilization has increased from 0.19 percent to 9 percent in the 310 patients reviewed. A reassessment of further candidates for atorvastatin demonstrated 10.6 percent of patients could be placed on atorvastatin due to unsafe combination regimens, aggressive LDL lowering needed, and failures on maximal simvastatin doses.

**Table 2. Atorvastatin candidates before and after interventions, according to Pharmacoeconomic Center guidelines**

<b>Therapeutic selection: atorvastatin as an alternative agent</b>	<b>Previous patient candidates for those on pharmacotherapy (n = 225)</b>	<b>Current patient candidates for those on pharmacotherapy (n = 310)</b>
LDL > 195 mg/dL or requiring > 50% LDL reduction	39 (17.3%)	5 (1.6%)
Not at LDL goal on maximal doses of simvastatin (80 mg)	7 (3.1%)	3 (9.7%)
Patients on unsafe combination therapy with simvastatin (dose > 10mg/day in combination with fibrates or niacin)	25 (11.1%)	21 (6.8%)
Patients on unsafe combination therapy with simvastatin (dose > 20mg/day in combination with amiodarone or verapamil)	Not collected previously	4 (1.3%)
Atorvastatin Utilization	1 (0.19%*)	28 (9%)
Further patient candidates for atorvastatin as an alternative agent	71 (31.6%)	33 (10.6%)

\*N = 527 (total population), including Category 1 patients

Figure 3 summarizes the barrier analysis in the baseline review compared to that from the follow-up review.

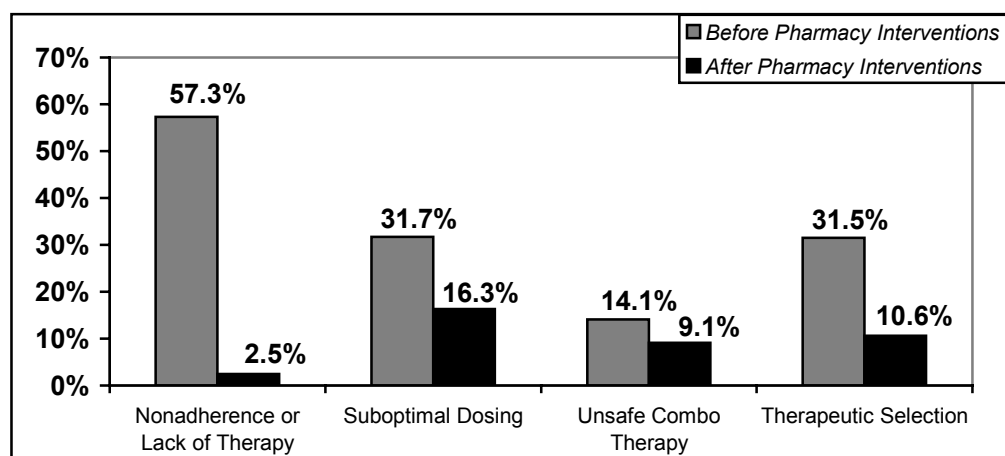
This improvement in LDL through medication safety initiatives, primarily focused on provider prescribing and enhancing safety through drug interactions among a large population of patients with dyslipidemia, would lead to a substantial savings (medical cost avoidance) in the form of reduced hospitalization expenditures, revascularization procedures or coronary artery bypass grafts (CABGs), physician visits, nursing services, stroke, mortality, and

other cardiovascular consequences. An internal estimate demonstrates approximately 60 deaths avoided through attainment of LDL goal in a population cohort of 310 patients evaluated. These avoided deaths project a cost avoidance and savings of approximately \$1.5 million over the next 5 years in just this population of patients included for review. Extrapolation of this figure to the over 6,000 patients identified from the baseline review as experiencing therapeutic failures suggests that the savings would be substantial.

## Conclusion

Pharmacy-gearred lipid interventions resulted in substantial improvements in cholesterol management and medication safety. This project has set the standard for collaboration between the Department of Defense, the pharmaceutical industry, and community providers to improve the health of our common beneficiaries. Current goal-attainment rates may serve as a baseline for a pharmacist-run lipid clinic that will be implemented at Patrick Air Force Base and possibly other military treatment facilities.

**Figure 3. Comparison of barrier analysis for therapeutic failures**



## Acknowledgments

The authors would like to acknowledge Rebecca H. Denning, Pfizer, Inc., Lt. Col. Beth Kohsin, U.S. Air Force Office of Patient Safety, and Karen Swisher, Virginia Commonwealth University, for their assistance and contributions during the preparation of this manuscript.

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